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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,233	01/13/2004	Poul Egon Bertelsen	5568.2CON(71432)	5334

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EXAMINER	
SASAN, ARADHANA	
ART UNIT	PAPER NUMBER
1615	
MAIL DATE	DELIVERY MODE
06/17/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/758,233	BERTELSEN ET AL.	
	Examiner	Art Unit	
	ARADHANA SASAN	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2010 and 25 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *68,70-72,75-80,82,83,85-96,108,109,111 and 115-126* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *68,70-72,75-80,82,83,85-96,108,109,111 and 115-126* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/12/10 and 6/11/10*.
4) ☐ Interview Summary (PTO-413) Paper No.(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. The remarks and amendments filed on 02/22/10 and 03/25/10 are acknowledged.

2. Claim 108 was amended.

3. Claims 68, 70-72, 75-80, 82, 83, 85-96, 108, 109, 111 and 115-126 are included in the prosecution.

Information Disclosure Statement

4. The information disclosure statements (IDS) submitted on 05/12/10 and 06/11/10 are acknowledged. Foreign patent documents JP 5-112445 and JP 5-271054 were not considered because they were not in English.

See attached copies of PTO-1449.

Response to Arguments

Claim Objections

5. In light of the amendment of claim 108, the claim objection is withdrawn.

6. Applicant's request (that upon indication of allowable matter and renumbering of the claims at the close of prosecution the Examiner reorder the claims such that the broader claims precede the narrower claims) is acknowledged.

MAINTAINED REJECTIONS:

The following is a list of maintained rejections:

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 68, 70-72, 75-80, 82, 83, 85-86, 91-92, 95-96, 108, 109, 111 and 119-126 **remain** rejected under 35 U.S.C. 103(a) as being unpatentable over Nemoto et al. (JP 03-240729) in view of Klioze et al. (US 2,887,439).

The claimed invention is a quick release pharmaceutical composition for oral administration comprising a therapeutically and/or prophylactically active substance which has a solubility of at the most 0.1% w/v in 0.1 N hydrochloric acid at room temperature, the composition being in the form of a particulate composition or being based on a particulate composition, wherein either the particles of the particulate composition used in the manufacture of the composition have a mean particle size of the most 250 micrometers, or at least 50% w/w of the particles of the particulate composition used in the manufacture of the composition pass through a 180 micrometer sieve; wherein the quick release pharmaceutical composition contains the active substance in contact with an alkaline substance; and the composition, when tested in accordance with the dissolution method I defined herein employing 0.07N hydrochloric acid as dissolution medium, releases at least 50% w/w of the active substance within the first 20 minutes of the test.

Nemoto teaches "an oral solid preparation containing one or more types of antacids that accelerates the absorption of oxicam antiinflammatory drugs" (Page 1, claim 1). Sodium hydrogen carbonate is disclosed as the antacid (Page 1, claim 3). The antacid "accelerates the absorption of oxicam antiinflammatory drugs" (Page 2).

Granules of the antacid and oxicam antiinflammatory drug are disclosed (Page 3). The granules are formed in a mixture of alcohol and purified water (Page 4). Capsules and tablets are manufactured by adding a lubricant to the granules (Page 4). The solubility of the prepared tablets in artificial gastric juice was greater than 50% within 20 minutes of the test (Page 9, Table 3). The granules were graded to 20 mesh (Page 5).

Nemoto does not expressly teach a mean particle size of at the most 250 micrometers of the granules.

Klioze teaches a tablet that may be swallowed whole, chewed, dissolved in the mouth, or dissolved or suspended in liquids (Col. 2, lines 6-12). This rapidly disintegrating tablet comprises a plurality of compressed granules containing sweetening agents and perhaps a filler (Col. 2, lines 13-20). The granules used in the tablets are screened "to insure that they are of an optimum size for the formation of tablets. It has been found that granules ranging from about 20 to 100 mesh (U.S. Sieve Series) are most advantageous in preparing the tablets of this invention" (Col. 2, lines 41-46). 20 mesh corresponds to 0.84mm or 840μm and 100 mesh corresponds to 0.149mm or 149μm (see Page 1544 of Remington's 16th Edition 1980, as provided by Applicant on 09/15/08). Therefore, Klioze teaches the formation of rapidly disintegrating tablets comprising granules that are between 149μm and 840μm, thereby rendering the instant claims with the limitation of the mean particle size of the particles of the particulate composition at the most 250μm obvious to one of ordinary skill in the art.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make an oral granule preparation containing an antacid and an

oxicam drug, as suggested by Nemoto, reduce the granule size to a range between 149μm and 840μm, as taught by Klioze, and produce the instant invention.

One of ordinary skill in the art would do this because Klioze teaches that granules ranging from about 20 to 100 mesh (or 149μm to 840μm) are most advantageous in preparing palatable, rapidly disintegrable tablets comprising compressed granules (as taught by Klioze). One of ordinary skill in the art would have a reasonable expectation of success in producing functional rapidly disintegrable tablets with granule size between 149μm to 840μm.

Regarding instant claims 68 and 70, the limitation of the active substance would have been obvious over the oxicams taught by Nemoto (Page 1, claim 1). The limitation of the active substance in contact with the alkaline substance and the limitation of a particulate composition would have been obvious over the granules of antacid and oxicam disclosed by Nemoto (Page 3). The limitation of the dissolution method employing 0.07N HCl acid as dissolution medium would have been obvious over the artificial gastric juice (with an acidic pH) taught by Nemoto (Page 9, Table 3). The limitation of the mean particle size of at the most 250 micrometers would have been obvious over the granules of antacid and oxicam disclosed by Nemoto (Page 3) in view of the final particle size of granules between 149μm and 840μm as taught by Klioze (Col. 2, lines 41-46).

Regarding instant claim 71, the limitation of at least 55% w/w release would have been obvious over the solubility of preparations 3-9 as disclosed by Nemoto (Page 9, Table 3).

Regarding instant claim 72, the solubility of the active substance would have been obvious over the oxicam actives taught by Nemoto (Page 1, claim 1).

Regarding instant claims 75-79, the limitation of an excipient would have been obvious over the calcium hydrogen phosphate taught by Nemoto (Page 6, Embodiment 9).

Regarding instant claim 80, the limitation of the particle size of the filler would have been obvious over the calcium hydrogen phosphate taught by Nemoto (Page 6, Embodiment 9). One with ordinary skill in the art would modify the particle size of the filler during the process of routine optimization and the recited particle size (140 μm) would have been an obvious variant unless there is evidence of criticality or unexpected results.

Regarding instant claims 82-83, 95-96 and 108, the antacid would have been obvious over the sodium hydrogen carbonate and calcium hydrogen phosphate disclosed by Nemoto (Page 1, claim 3). The limitation of the mean particle size of the antacid-like substance would have been obvious because one with ordinary skill in the art would vary the particle size of the antacid during the process of routine experimentation depending on the desired attributes of the composition and over the final particle size of granules between 149μm and 840μm as taught by Klioze (Col. 2, lines 41-46). The recited particle size (at the most 297 μm) would have been an obvious variant unless there is evidence of criticality or unexpected results.

Regarding instant claims 85-86, the active substance would have been obvious over the piroxicam and tenoxicam disclosed by Nemoto (Page 2, 3rd paragraph).

Regarding instant claims 91-92, the dosage of the active substance would have been obvious over the 2mg of chlortenoxicam and tenoxicam disclosed by Nemoto (Page 5, Table 1).

Regarding instant claim 109, the dissolution test would have would have been obvious over the artificial gastric juice (with an acidic pH) taught by Nemoto (Page 9, Table 3). A person skilled in the art would have found it obvious to test the dissolution/release of the active at various pH levels (especially acidic pH levels which are present in gastric conditions) during the process of routine optimization to ensure the release of the active ingredient.

Regarding instant claim 111, the coated tablet would have been obvious over the coating of tablets taught by Nemoto (Page 4, 2nd full paragraph).

Regarding claims 119-120, the limitation of the composition having mechanical strength to enable the composition to be coated using traditional coating equipment would have been obvious over the coating of tablets taught by Nemoto (Page 4, 2nd full paragraph).

Regarding claims 121-122, the limitation of the composition further comprising a filler having binding properties would have been obvious over the calcium hydrogen phosphate disclosed by Nemoto (Page 1, claim 3). The crushing strength limitation is a functional limitation which is rendered obvious by the tablet comprising granules as taught by Nemoto in view of the granules taught by Klioze. One of ordinary skill in the art would find it obvious to determine the crushing strength of the tablets during the process of routine experimentation and the recited crushing strength of at least about

50N would have been an obvious variant unless there is evidence of criticality or unexpected results.

Regarding instant claims 123-124, the limitation of the composition that passes through a 180 micrometer sieve would have been obvious over the granules that are between 149μm and 840μm, as taught by Klioze (Col. 2, lines 41-46).

Regarding instant claims 125-126, the limitations of the granulate would have been obvious over the granules of the antacid and oxicam antiinflammatory drug taught by Nemoto (Page 3).

9. Claims 87-90, 93-94 and 115-118 **remain** rejected under 35 U.S.C. 103(a) as being unpatentable over Nemoto et al. (JP 03-240729) in view of Klioze et al. (US 2,887,439) and Penkler et al. (US 5,854,226).

The teachings of Nemoto and Klioze are stated above.

Nemoto and Klioze do not expressly teach lornoxicam as the active substance.

Penkler teaches a pharmaceutical composition for oral administration comprising an inclusion complex of a non-steroidal anti-inflammatory drug, including lomoxicam (Col. 5, lines 66-67), an alkaline earth metal bicarbonate, and further active ingredients (Abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make an oral granule preparation containing an antacid and an oxicam drug, as suggested by Nemoto, reduce the granule size to a range between 149μm and 840μm, as taught by Klioze, use lornoxicam as the drug along with an

alkaline earth metal bicarbonate, as suggested by Penkler, and produce the instant invention.

One of ordinary skill in the art would do this because the use of lornoxicam in a pharmaceutical composition with an alkaline earth metal bicarbonate is known, as evidenced by Nemoto and Penkler. One with ordinary skill in the art would find it obvious to substitute lornoxicam for the oxicams used by Nemoto during the process of routine experimentation with a reasonable expectation of success in producing a functional pharmaceutical composition comprising lornoxicam and an alkaline earth metal bicarbonate.

Regarding instant claim 87, the limitation of the lornoxicam would have been obvious over the lornoxicam taught by Penkler (Col. 5, lines 66-67).

Regarding instant claims 88-90, the further active drug substance would have been obvious over the further active drug substance, including paracetamol as taught by Penkler (Col. 8, lines 9-12).

Regarding instant claim 93, the dosage of the active substance would have been obvious over the unit compositions of lornoxicam (4mg) taught by Penkler (Figure 2). One with ordinary skill in the art would vary the dosage of the active ingredient, lornoxicam, in order to optimize the release/dissolution profile, and stability.

Regarding instant claim 94, the water content limitation would have been obvious over the drying step (after the addition of water and mixing steps) as taught by Penkler (Col. 4, line 9). A person skilled in the art would reduce the water content of the composition in order to improve shelf life and minimize interactions and leaching,

therefore, the water content limitation would have been an obvious variant found during routine optimization.

Regarding new claims 115-118, the limitation of lornoxicam would have been obvious over the lornoxicam taught by Penkler (Col. 5, lines 66-67). The limitation of sodium hydrogen carbonate would have been obvious over the sodium hydrogen carbonate disclosed by Nemoto (Page 1, claim 3). The limitation of microcrystalline cellulose would have been obvious over the microcrystalline cellulose disclosed by Nemoto (Page 5, Table 1). The limitation of calcium hydrogen phosphate anhydrous would have been obvious over the calcium hydrogen phosphate disclosed by Nemoto (Page 1, claim 3). The limitations of L-HPC and hydroxy propyl cellulose would have been obvious over the low substituted hydroxypropyl cellulose and the hydroxypropyl cellulose disclosed by Nemoto (Page 5, Table 1). The limitations of water and ethanol would have been obvious over the mixture of alcohol and purified water disclosed by Nemoto (Page 4, lines 5-6). The limitation of calcium stearate would have been obvious over the calcium stearate disclosed by Nemoto (Page 4, line 12).

Response to Arguments

10. Applicant's arguments, see Page 8, filed 02/22/10, with respect to the following rejections have been fully considered but are not persuasive.

- Rejection of claims 68, 70-72, 75-80, 82, 83, 85-86, 91-92, 95-96, 108, 109, 111 and 119-126 under 35 U.S.C. 103(a) as being unpatentable over Nemoto et al. (JP 03-240729) in view of Klioze et al. (US 2,887,439)

- Rejection of 87-90, 93-94 and 115-118 under 35 U.S.C. 103(a) as being unpatentable over Nemoto et al. (JP 03-240729) in view of Klioze et al. (US 2,887,439) and Penkler et al. (US 5,854,226)

Applicant argues that "there can be no motivation to combine Nemoto and Klioze, either with or without the teachings of Melia. The prior rejection would not have included Melia if the combination of references could have been made without Melia."

This is not persuasive because the rejection with Melia as a supporting reference was withdrawn in favor of the rejection over the combination of Nemoto and Klioze. Since this was a new ground of rejection, the previous office action was a non-final rejection.

Nemoto and Klioze are properly combined because both references are directed to rapid action compositions. Nemoto teaches rapid action, i.e., **rapid absorption such as for toothache** (Page 4, [Effect of the Invention]) and Klioze teaches **rapidly disintegrable** tablets (Col. 1, lines 15-18) and tablets that can be "**dissolved in the mouth, or dissolved or suspended in liquids** such as milk and fruit juices ..." (emphasis added, Col. 2, lines 6-12). Not only are the tablets of Klioze **rapidly disintegrable**, they are also **rapidly dissolvable**.

Applicant argues that dissolution rate is not the same as disintegration rate, that Klioze is not concerned with a dissolution rate, and that Klioze is concerned with a disintegration rate.

This is not persuasive because Klioze teaches **rapidly disintegrable** and **rapidly dissolvable** tablets.

Applicant argues that Nemoto and Klioze must be considered for what they teach as a whole. Applicant argues that "despite the teaching that smaller granules can be used for the preparation of tablets, larger granules are preferred ... one reading the reference as a whole would not suggest to one of skill in the art at the time of filing of the instant application to use a smaller granule size."

This is not persuasive because patents are relevant as prior art for all they contain. "The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain ... A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments." Please see MPEP 2123. Since Klioze clearly discloses granules that are between 149μm to 840μm that are used for **rapidly disintegrable** and **rapidly dissolvable** tablets, one of ordinary skill in the art would be motivated to use granules in this size range for tablets designed for **rapid disintegration, rapid dissolution**, rapid action, and/or rapid onset.

Applicant argues that if Nemoto were concerned only with dissolution, Nemoto would simply increase the amount of antacid.

This argument regarding what Nemoto would have done is speculative. There is no evidence that Nemoto would only manipulate the amount of antacid in order to modify dissolution.

Applicant argues that one reading Nemoto in view of Klioze would not be inclined to use smaller granules, or to modify the size or method for making granules as each

provides only a single method for making tablets (although the tablets of Klioze do include granules of different sizes).

This is not persuasive because, as Applicant points out, Klioze discloses granules that are between 149μm to 840μm, which are used for **rapidly disintegrable** and **rapidly dissolvable** tablets, thereby providing motivation for one of ordinary skill in the art to use granules in this size range for tablets designed for **rapid disintegration and/or rapid dissolution**.

Applicant argues that "Nemoto and Klioze must be considered in view of the totality of the art at the time of filing of the instant application. Applicant has provided multiple references throughout the prosecution of the instant application to demonstrate that one of skill in the art would not consider reduction of granule size or the use of granules of the sizes claimed to be advantageous in the preparation of pharmaceutical compositions." Applicant points to *In re Hedges*, et al., 228 USPQ 685 (Fed. Cir. 1986). Applicant argues that the instantly claimed invention is contrary to the accepted wisdom and is not obvious in view of the cited art and that "when making tablets based on the teachings of Nemoto, one would look to tablet forming machines and technologies available to Nemoto, not tablet forming methods of Klioze."

The arguments and references provided by Applicant have been fully considered but are not persuasive because one of ordinary skill in the art at the time the invention was made would have found it obvious to look at **all pertinent art**, including art directed to rapidly disintegrable and rapidly dissolvable tablets, such as disclosed by Klioze.

Applicant submits that one of skill in the art would not [be] likely to rely on a reference from forty years earlier when considering the field of preparation of pharmaceutical compositions.

In response to applicant's argument based upon the age of the references, contentions that the reference patents are old are not impressive absent a showing that the art tried and failed to solve the same problem notwithstanding its presumed knowledge of the references. See *In re Wright*, 569 F.2d 1124, 193 USPQ 332 (CCPA 1977). Klioze teaches the incorporation of granules with a size between 149µm to 840µm in rapidly disintegrable and rapidly dissolvable tablets. One of ordinary skill in the art would find it obvious to look at all pertinent art regarding rapidly disintegratable and rapidly dissolvable tablets and their particular granule size.

Applicant argues that "...reducing granule size would provide material less desirable for tableting. Decreasing the granule size of Nemoto to the size instantly claimed would likely result in poor flow characteristics, resulting in tableting difficulties."

This is not persuasive because Klioze clearly demonstrates successful tableting with granules that are between 149µm to 840µm. Klioze does not disclose any difficulties or drawbacks with using granules of this particular size range.

The prior art reference (Klioze) teaches the same objective as sought by Applicant.

Applicant argues that granule size is not a result-effective variable for dissolution and that the Examiner has failed to provide a reference demonstrating that one of skill in the art would understand granule size to be a result-effective variable in relation to

dissolution. Applicant argues that modulation of dissolution properties by modulation of granule size is not routine.

This is not persuasive because there is a clear teaching in the prior art that granules of the size range 149μm to 840μm can be incorporated successfully in tablet formulations, and these tablets provide not only rapid disintegration, but also rapid dissolution in the mouth and other fluids (such as milk or fruit juices).

Therefore, the rejection of 11/23/09 is maintained.

Conclusion

11. No claims are allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aradhana Sasan whose telephone number is (571) 272-9022. The examiner can normally be reached Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax, can be reached at 571-272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Aradhana Sasan/
Examiner, Art Unit 1615

/Humera N. Sheikh/
Primary Examiner, Art Unit 1615